

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/806,829 Confirmation No.: 4240  
Applicant : Jian Bai, Steven M. Fischer and J. Michael Flanagan  
Filing Date : March 22, 2004  
Title : Ambient Pressure Matrix-Assisted Laser Desorption Ionization  
(MALDI) Apparatus and Method of Analysis  
Group Art Unit : 2881  
Examiner : Nikita Wells  
Docket No. : 10980322-4 (12089.4003)  
Customer No. : 022878

Commissioner For Patents  
Mail Stop AMENDMENT  
P.O. Box 1450  
Alexandria, VA 22313-1450

**RESPONSE TO ACCOMPANY RCE**

Sir:

Claims 34-80 are pending in this application. Claims 1-33 have been cancelled without prejudice. This response replies to the only remaining issue in the patent case, i.e., whether the specification supports the claim limitation “without additional matrix. . .” pursuant to the written description requirement of 35 U.S.C. §112 ¶1.

The attached declaration of Steven M. Fischer establishes that the present specification supports the claim limitation at issue and the pending claims are now allowable.

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1-33. (Cancelled)

34. (Previously Presented) A method for mass spectroscopic analysis of an analyte solution, comprising:

irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution, with a light beam to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;

transferring said gas-phase ions to a mass analyzer; and

mass-analyzing said gas-phase ions by said mass analyzer.

35. (Previously Presented) The method as in claim 34, wherein the step of irradiating with a light beam comprises:

irradiating with a laser beam.

36. (Previously Presented) The method as in claim 35, wherein the step of irradiating with a laser beam comprises:

pulsing with a laser beam.

37. (Previously Presented) The method as in claim 36, wherein the step of irradiating comprises:

producing said gas-phase ions at or about atmospheric pressures.

38. (Previously Presented) The method as in claim 34, wherein the step of transferring comprises:

transferring said gas-phase ions to an inlet port of a mass spectrometer equipped with an atmospheric pressure interface.

39. (Previously Presented) The method as in claim 34, further comprising:

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depositing said analyte solution on a surface, prior to the step of irradiating.

40. (Previously Presented) The method as in claim 39, wherein the step of depositing comprises:

depositing a matrix-free analyte solution.

41. (Previously Presented) The method as in claim 38, wherein said step of depositing comprises:

depositing said analyte solution on at least one of metal surface, and a membrane.

42. (Previously Presented) The method as in claim 34, wherein said analyte solution is in an electrophoresis gel.

43. (Previously Presented) The method as in claim 39, wherein said step of depositing comprises:

depositing said analyte solution on a flat surface.

44. (Previously Presented) The method as in claim 39, wherein said step of depositing comprises:

depositing samples of multiple analyte solutions on an array.

45. (Previously Presented) The method as in claim 34, wherein said step of transferring comprises:

placing said analyte solution close to at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.

46. (Previously Presented) The method as in claim 34, wherein said step of transferring comprises:

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generating an electric field between said analyte solution and at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port to assist in transfer of said gas-phase ions into the mass analyzer.

47. (Previously Presented) The method as in claim 34, wherein said step of transferring comprises:

producing a gas flow to transfer said gas-phase ions toward at least one of an inlet port of said mass analyzer and an inlet orifice attached to said inlet port.

48. (Previously Presented) The method as in claim 34, wherein said step of mass-analyzing comprises:

analyzing liquid solutions of organic and inorganic compounds including peptides, proteins, nucleic acids, polymers and other compounds of biological significance.

49. (Previously Presented) The method as in claim 34, wherein said step of irradiating comprises:

irradiating said analyte solution at a wavelength which is absorbed by said analyte solution.

50. (Previously Presented) The method as in claim 39, further comprising:  
providing a liquid flow of said analyte solution to said surface.

51. (Previously Presented) A system for the mass spectroscopic analysis of an analyte solution, comprising:

means for irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;

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means for mass-analyzing said gas-phase ions; and

means for transferring said gas-phase ions into said means for mass-analyzing.

52. (Previously Presented) The system as in claim 51, further comprising:

means for depositing said analyte solution on a surface.

53. (Previously Presented) The system as in claim 52, wherein said means for depositing is configured to deposit a matrix-free analyte solution.

54. (Previously Presented) The system as in claim 52, wherein said surface comprises:

at least one of a metal surface and a membrane.

55. (Previously Presented) The system as in claim 52, wherein said surface comprises an electrophoresis gel.

56. (Previously Presented) The system as in claim 52, wherein said surface comprises an array of multiple analyte solutions.

57. (Previously Presented) The system as in claim 51, wherein said means for transferring comprises:

an electric field between said analyte solution and an inlet of said means for mass analyzing to assist in transfer of said gas-phase ions into the means for mass analyzing.

58. (Previously Presented) The system as in claim 51, wherein said means for irradiating a surface comprises:

means for irradiating at a wavelength which is absorbed by said analyte solution.

59. (Previously Presented) The system as in claim 51, wherein said means for irradiating comprises:

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means for pulsing an infrared laser light.

60. (Previously Presented) The system as in claim 52, further comprising:

means for providing a liquid flow of said analyte solution to said surface.

61. (Previously Presented) The system as in claim 54, wherein said means for providing comprises:

means for moving said surface.

62. (Previously Presented) The system as in claim 54, wherein said means of providing comprises:

means for moving said surface relative to said means for mass analyzing.

63. (Previously Presented) The system as in claim 54, wherein said means for providing comprises:

means for providing a continuous flow of the analyte solution.

64. (Previously Presented) The system as in claim 51, wherein said means for transferring comprises:

an enclosure with a gas under defined pressure and temperature conditions.

65. (Previously Presented) An apparatus for the mass spectroscopic analysis of an analyte solution, comprising:

a light source configured to irradiate a liquid volume of said analyte solution, without additional matrix added to said analyte solution, to desorb solution-specific ions into a surrounding gas to produce gas-phase ions;

a mass analyzer configured to mass-analyze said gas-phase ions; and

means to transfer said gas-phase ions to said mass analyzer.

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66. (Previously Presented) The apparatus as in claim 65, wherein the light source comprises a laser beam.

67. (Previously Presented) The apparatus as in claim 66, wherein the laser beam is configured to generate a pulsed laser beam.

68. (Previously Presented) The apparatus as in claim 65, wherein said gas-phase ions are produced at or about atmospheric pressures.

69. (Previously Presented) The apparatus as in claim 65, wherein the transfer mechanism includes an inlet port on a mass spectrometer equipped with an atmospheric pressure interface.

70. (Previously Presented) The apparatus as in claim 65, further comprising: a substrate configured to receive said analyte solution.

71. (Previously Presented) The apparatus as in claim 70, wherein said surface comprises:

at least one of a metal surface and a membrane.

72. (Previously Presented) The apparatus as in claim 70, wherein said surface comprises an electrophoresis gel.

73. (Previously Presented) The apparatus as in claim 70, wherein said surface comprises:

an array with multiple analyte solutions.

74. (Previously Presented) The apparatus as in claim 65, wherein said mass analyzer comprises:

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at least one of an inlet orifice attached to an inlet port of a mass spectrometer and a capillary tube attached to said inlet port.

75. (Previously Presented) The apparatus as in claim 65, wherein the transfer means comprises:

an electric field between said analyte solution and at least one of an inlet port and a capillary tube attached to said inlet port.

76. (Previously Presented) The apparatus as in claim 65, wherein the analyte solution comprises:

a liquid solution including at least one of peptides, proteins, nucleic acids, polymers and other compounds of biological industrial significance.

77. (Previously Presented) The apparatus as in claim 65, wherein said light source is configured to irradiate said analyte solution with laser pulses at a wavelength which is absorbed by the analyte solution.

78. (Previously Presented) The apparatus as in claim 65, further comprising a high-performance liquid chromatograph or a CE.

79. (Previously Presented) The apparatus as in claim 65, further comprising:  
an enclosure filled with a gas under atmospheric pressure.

80. (Previously Presented) The apparatus as in claim 65, wherein said analyte solution comprises:

a matrix-free analyte solution.

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## RESPONSE

All prior art based objections have been resolved and the lone remaining issue is the adequacy of the present specification to satisfy the written description under §112, specifically for the claim element:

“irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution...”

The declaration of Steven M. Fischer establishes that one of ordinary skill in the art would understand that the present specification discloses the step of irradiating a liquid volume of analyte solution “without additional matrix added to said analyte solution.”

This language describes performing MALDI directly on a sample analyte in solution such that the laser is chosen specifically for the solution containing the analyte and such that ionization of the analyte occurs by direct charge transfer from the irradiated solution to the analyte. Under such circumstances, no additional matrix is necessary or desirable.

A. The Present Specification Describes The Combination of a Chromatography Apparatus and a Mass Spectrometer Such that a Liquid Analyte Solution Is Irradiated to Yield Ionized Analyte Without The Necessity of Additional Matrix.

The disclosure of the present specification describes liquid analyte solution without additional matrix to the extent necessary for one of ordinary skill in the art to understand that the inventors were in possession of this subject matter. The following excerpts from the specification clearly describe the absence of “additional matrix” added to said analyte solution:

“Flowing” refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed.

(See specification page 10, lines 20 – 21 and here after “Spec 10:20 – 21”)

“Holder” also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like.

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(Spec 10:25-27)

The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice.

(Spec 13:2-3)

The sampling may occur using a static or a flowing liquid sample, such as the effluent from an HPLC, CE, or syringe pump.

(Spec 13:8-10)

These examples disclose that the liquid undergoing chromatographic separation contains the analyte, and that the liquid is the matrix. No requirement for any added matrix exists and none is described.

Thus, when the present specification discloses irradiation of a flowing liquid solution containing analyte, the specification is describing an analyte solution without added matrix because the solution transfers charge to (or from) an analyte, and thereby acts as the matrix.

B. One of Ordinary Skill In the Art Would Understand The Definition of “Matrix” Including a Liquid and Matching The Laser Wavelength to Achieve Charge Transfer As Written Description of Irradiating Liquid Solution Containing Analyte Without “Additional Matrix.”

1. The express language of the specification describes the element at issue.

The present specification does not require that any matrix be added to the analyte solution. The present specification defines “matrix” as:

“Matrix” refers to any solid or liquid molecules having the ability to transfer or receive a charge from the analyte and an absorption of the wave length of the laser ...

\* \* \*

For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive

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a charge from the analyte are suitable. (Spec. 11:1-8) (emphasis added)

Thus, the express definition of “Matrix” in the specification conveys to one skilled in the art that molecules of the liquid solution cause charge transfer that ionizes the analyte in solution without the need for any “additional matrix.”

2. The disclosure of a liquid solution at atmospheric pressure tells one of ordinary skill that no additional matrix is needed.

In addition to the plain text of the specification, the entire content of the specification is the disclosure of the novelty of AP MALDI compared to the prior art vacuum MALDI. One of the advantages is the ability to physically attach a mass spectrometer to a chromatography apparatus so that analytes can be chromatographically separated and then directly fed into a mass spectrometer. See Fischer declaration at ¶ 6.

Accordingly, the specification would be read by one of ordinary skill as disclosing that one of the many advantages of AP MALDI is advantageous analyte preparation, and specifically, that the use of a chromatography solvent as the matrix-charge transfer agent means that the irradiation and charge transfer processes take place in the solvent and thus does not require any “additional matrix.”

Furthermore, the present application discloses the specific and selective pairing of the laser wavelength to the liquid such that the analyte solvent acts as the matrix and thereby describes performing the irradiation in a solution “without additional matrix.” The specification states.

“Matrix” refers to any solid or liquid molecules having the ability to transfer or receive a charge from the analyte and an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof. For an ultraviolet laser,

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substituted aromatic compounds are used which can transfer or receive a charge to or from the analyte. For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable.

Water is the predominant chromatography solvent used in the art and it is specifically disclosed in the present specification as a "matrix." By selecting the wavelength of the laser to be suitable for the solvent, no additional matrix is needed.

Accordingly, a description of the direct ionization of analyte in solution is a written description of the element at issue and the disclosure of the required solvent(s), laser(s) and utility in mass analysis contained in the present specification meets the written description requirement of §112. Therefore, to one skilled in the art, the present specification describes the absence of added matrix claimed step of "irradiating a liquid volume of said analyte solution, without additional matrix added to said analyte solution" by disclosing the step of irradiating the analyte in the liquid sample with a laser paired to the solvent.

C. The Present Specification Satisfies the Legal Standard Governing the Written Description Requirement of §112 for the Step of Irradiating a Liquid Analyte Solution Without Additional Matrix.

As noted above, the specification describes an analyte solution without additional matrix because: first, the specification discloses that the analyte contained in solution can be ionized by irradiating the solution itself and that where the analyte is ionized directly by the solution, no additional matrix is used; and second, the specification expressly defines the solution containing the analyte as a "matrix" that facilitates ionization of the analytes in the solution.

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1. The negative limitation “without additional matrix” need not be written verbatim in the specification – a description of irradiation of a liquid solution containing analyte under condition to create change transfer is sufficient.

The law does not require that the terms “without additional matrix” appear verbatim in the specification. The purpose of the written description requirement is to confirm that the inventor “possesses” the invention as of the time of the application. In re Johnson, 558 F.2d 1008, 1018 (CCPA 1977). The proper focus of the inquiry is whether the specification adequately supplies formulas, charts, diagrams or any other material from which one skilled in the art can ascertain that the inventor “possessed,” or invented, the subject matter of the claim. As the court held in In re Smith, 481 F.2d 910 (CCPA 1973):

The specification as originally filed must convey clearly to those skilled in the art information that the applicant has invented the subject matter later claimed. [Citations omitted] When the original specification accomplishes that, regardless of how it accomplishes it, the essential goal of the description requirement is realized.

“The written description requirement is satisfied by the patentee’s disclosure of ‘such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention.’” Crown Operations International Ltd. V. Solutia Inc., 289 F.3d 1367, 1376 (Fed. Cir. 2002).

The present specification makes clear at least the following beyond dispute” 1) the analyte may be contained in a liquid matrix that performs the change transfer function; 2) the laser wavelength is matched to the analyte solvent so that the solvent functions as the matrix; 3) the AP MALDI technique can be applied to flowing analyte in solution and at atmospheric pressure without adding matrix; and 4) the direct coupling of a chromatography apparatus and

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mass spectrometer enables mass analysis without the additional analyte/sample process where additional matrix would be used. Thus, the present specification supports the claim limitation at issue.

2. The '300 patent contains the same written description for the claim element at issue.

Applicants submit that there is no construction of the element at issue based on the 6,683,300 patent that would alter the plain meaning of the claimelement or preclude the present specification from satisfying the §112 written description requirement for the claim element at issue. The '300 patent has no verbatim disclosure of the phrase “without additional matrix. . . “ and simply describes the same method of irradiating analyte in liquid solution as the present specification.

The method and system include the steps of or means for irradiating a liquid volume of the analyte solution with a light beam resulting in desorption of solution-specific ions into a surrounding gas to produce gas-phase ions, transferring the gas-phase ions to a mass, and mass-analyzing the gas-phase according to a mass to charge ratio.

'300 Patent, col. 4, lines 55 – 61

Ambient pressure ionization is achieved by irradiating the aqueous solutions with a pulsed laser at an absorption wavelength of the solution.

Id. at col. 5, lines 4 – 6

In accordance with the present invention, ions are produced at or about atmospheric pressure directly from an analyte solution which is deposited as a droplet from an atop of a solid target plate.

Id. at col. 5, lines 13 – 16

The analyte solution can include water, organic fluids, inorganic fluids, or a mixture thereof. The analyte solution can include solutions or organic and inorganic compounds including at least

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one of peptides, proteins, nucleic acids, polymers, drugs, and other compounds of biological, medical or industrial significance.

Id. at col. 6, lines 1 – 6

According to the present invention, the AP LADI method can be used for MS analyses of other liquid solutions such as the common analyte solutions previously discussed. The droplet size, laser pulse energy, and target plate material and/or coating are adjusted according to the present invention to optimize ionization efficiency for the type of solvent employed.

Id. at col.11, lines 4 – 9

The mass spectrometer interface according to the present invention can be modified so that a continuous flow of a liquid solution (e.g., from a high pressure liquid chromatography HPLC or capillary electrophoresis CE) is supplied directly to the laser spot position.

Id. at col. 11, lines 31 – 35 (emphasis added)

A liquid solution 38 that is to be mass-analyzed is supplied through a capillary transfer tube 37, connected at one end to a liquid pump such as for example a syringe pump, a liquid chromatography instrument pump, an output of capillary zone electrophoresis installation, or any other device that can provide a liquid analyte solution flow.

Id. at col. 11, lines 46 – 52

These examples show that the construction and support for the terms “without additional matrix added to said analyte solution” element in the ’300 patent should be the same as in the present specification. In both cases, the specification describes irradiation of analyte solution and the production of ions directly from the analyte solution. Therefore, the disclosure of this element in the present specification complies with the written description requirement of §112.

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### CONCLUSION

Applicant submit that the support for the claim element at issue is more than sufficient to meet the standard of 35 U.S.C. §112 and that the pending claims recite patentable subject matter in common with USP 6,683,300.

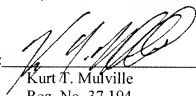
Should the Examiner have any questions or comments, the undersigned can be reached at (949) 567-6700. The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 150665.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: August 25, 2009

By: \_\_\_\_\_

  
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